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Lymph Node Status Assessment for Gastric Carcinoma: Is the Number of Metastatic Lymph Nodes Really Practical as a Parameter for N Categories in the TNM Classification?

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Background and Objectives: The anatomical extent of nodal metastasis has been replaced by the number of metastatic nodes as a key indicator of prognosis (pN categories) in the fifth edition of Tumor Node Metastasis Classification for gastric carcinoma by the International Union Against Cancer. The rate of metastatic nodes among all the nodes harvested is also a good prognostic factor. The object of this study is to evaluate which of the three parameters for the assessment of nodal status is the most appropriate for use in the stage classification.

Methods: Retrospective survival analyses were performed in 656 consecutive patients with advanced gastric carcinoma who underwent D2 lymphadenectomy and for whom histopathologic data of more than 20 lymph nodes were available.

Results: Although all three systems served well to classify the patients into distinct groups in terms of survival curves, stratification by the number of metastatic nodes was vulnerable to stage migration because of differences in the number of lymph nodes harvested. Such stage migration was not evident for the other two parameters.

Conclusions: Lymph node metastatic rate can be recommended as an internationally applicable parameter for lymph node involvement of gastric carcinoma. *J. Surg. Oncol. 1998;69:15–20.*

KEY WORDS: prognosis; survival curve; stage classification

INTRODUCTION

The absence or presence and anatomical extent of lymph node metastasis are significant prognostic factors for gastric carcinoma [1,2]. These factors, expressed in terms of pN categories proposed by the International Union Against Cancer (UICC) [3] or n categories proposed by the Japanese Society for Gastric Cancer Study in the Japanese Classification of Gastric Carcinoma (JCGC) [4], have served as an essential component of the widely acclaimed stage classifications for gastric carcinoma. However, the anatomical extent of nodal metastasis cannot be assessed with accuracy unless sufficient systematic lymphadenectomy is performed. In most Western institutions where the extended lymphadenectomy is not recognized as a standard treatment for gastric carcinoma [5,6], the n or pN categories may not have been practical as a key parameter for a stage classification scheme.

Recently, the UICC decided to replace these with the number of metastatic lymph nodes, another promising

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prognosticator [7,8] as new pN categories in their latest version of the Tumor Node Metastasis (TNM) Classification [9]. The authors have recently shown that the rate of metastatic nodes among all the nodes resected is a significant prognostic factor for stage IV gastric carcinoma [10]. In this retrospective study involving 656 patients with advanced gastric carcinoma, we attempted to evaluate the feasibility of the three modes of lymph node status assessment.

PATIENTS AND METHODS

During the 10-year period between 1983 and 1992, 1913 patients with gastric carcinoma underwent surgery at Aichi Cancer Center Hospital. Of these, 656 consecutive patients who fulfill the following criteria were selected: (1) carcinoma invaded beyond the muscularis propria (i.e., advanced carcinoma); (2) extended lymphadenectomy had been performed; and (3) retrieval followed by histopathologic evaluation of no less than 20 lymph nodes had been accomplished. The age of the patients ranged from 24 to 91 years, with a mean and standard deviation of 59.6 ± 11.2. Of these patients, 417 (63.6%) were male. The surgical procedures performed were total gastrectomy in 250, proximal gastrectomy in 25, distal gastrectomy in 379, and pancreaticoduodenectomy in 2. The extent of lymphadenectomy was D2 in 543 and more extensive in 113. Lymph nodes were immediately sent postoperatively for hematoxylin and eosin staining and histopathological examination. Numbers of resected and metastatic lymph nodes from each anatomical region as defined by the JCGC were recorded.

On the basis of the data thus obtained, stratifications according to three different modes of lymph node status assessment were performed. The first of these was the absence or presence and extent of nodal metastases (n categories), defined by the JCGC [4]. In the n categories, n0 denotes absence of node metastasis, while n1 signifies metastasis mainly to the perigastric nodes and n2 denotes more extensive metastasis within the regional lymph nodes. n3 and n4 that are collectively treated as > n3 in the current study (n3 denotes involvement of hepatoduodenal, mesenteric, or retropancreatic nodes, and n4 signifies involvement of para-aortic nodes) have been defined as distant metastases (pM1) in the TNM classification, with the exception of metastatic nodes along the hepatoduodenal ligament (No.12 node), which is defined as one of the regional lymph nodes by the TNM classification [11]. The stratification in terms of number of metastatic nodes was performed according to the fifth edition of TNM classification [5], in which carcinoma with no metastatic nodes is defined as pN0, those with 1–6 metastatic nodes is defined as pN1, 7–15 nodes as pN2, and more than 15 nodes as pN3. Finally, stratification into four groups according to the lymph node metastatic rate (the number of metastatic lymph nodes divided by the number of retrieved lymph nodes ×100) was performed as follows; carcinoma with a nodal metastatic rate of 0%, 1–19 %, 20–60%, and >60%.

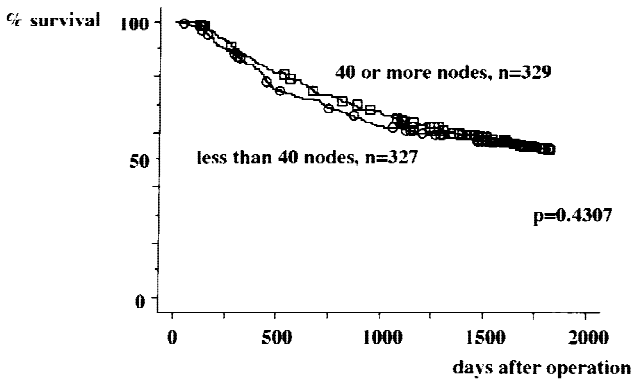

Fig. 1. The patients were divided into two groups according to the number of lymph nodes resected. Nodal yields for group A patients (n = 327) ranged from 20 to 39, while that for group B patients (n = 329) was 40 or more. Survival curves for the two groups were almost identical.

In order to evaluate the influence of the number of lymph nodes harvested on each of the nodal status assessments, the patients were then classified into two groups according to the nodal yields; the patients with nodal yields of less than 40 (group A, n = 327) and those with yields of 40 or more (group B, n = 329). There was no significant difference (P = 0.2383 by chi-square test) in the frequency of noncurative operation (n = 39 for group A and n = 29 for group B) between the groups. The number of patients belonging to the clinical stages defined by the JCGC were also similarly distributed for the two groups (69 stage I, 61 stage II, 125 stage III, and 72 stage IV patients for group A and 43 stage I, 88 stage II, 132 stage III, and 66 stage IV patients for group B). The lack of difference in these background factors is reflected in the survival curves that were almost identical for groups A and B (Fig. 1). The survival curves for groups A and B were then compared within several subgroups as stratified according to the three different modes of lymph node status assessment described above.

Statistical Analysis

All the patients in this study were followed until April 1, 1997, or until death. Deaths by causes other than gastric carcinoma recurrence are treated as censored cases. The Kaplan-Meier method was used to plot the survival curves, and the generalized Wilcoxon test was employed to evaluate the differences between these curves. Student's *t*-test was performed for comparison of number of metastatic lymph nodes between the two groups. The correlation between the number of metastatic lymph node and lymph node metastatic rate was assessed by Pearson's correlation coefficient.

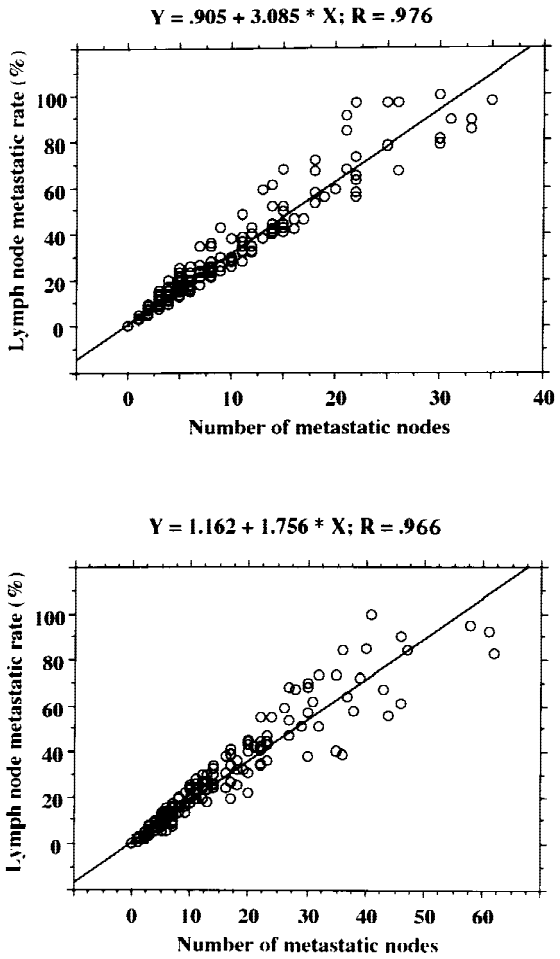

Fig. 2. The correlation between the number of metastatic nodes and lymph node metastatic rate was statistically significant ($P < 0.0001$) both for group A (top) (n = 327) and for group B (bottom) (n = 329) patients.

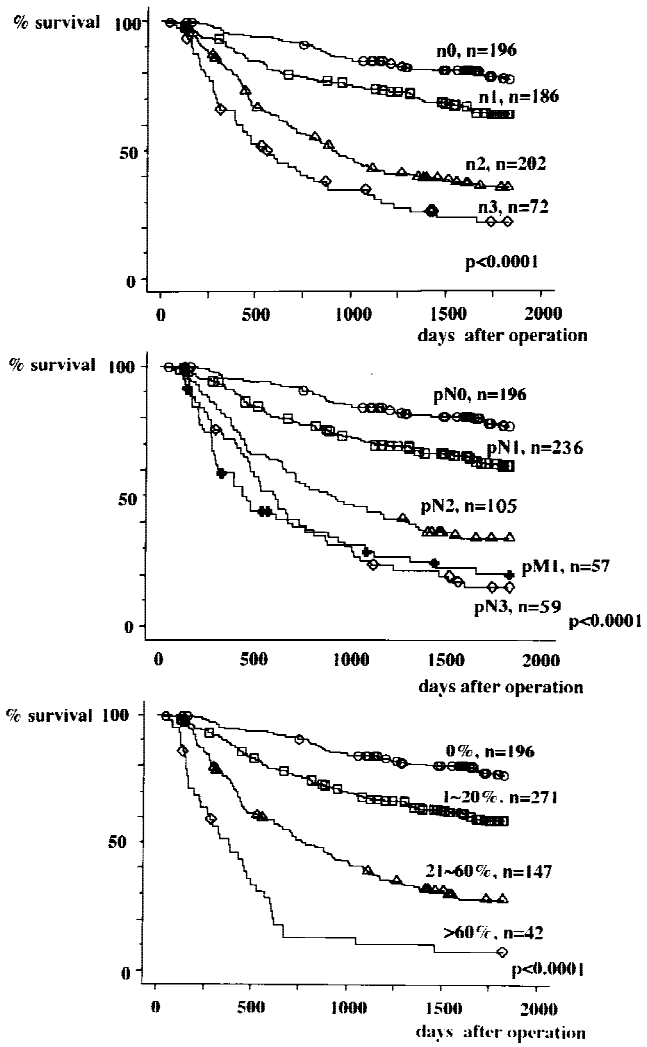

Fig. 3. Lymph node status assessment in terms of n categories by the Japanese Classification for Gastric Carcinoma (top), pN categories by the TNM Classification (middle), and the rate of the metastatic lymph nodes (bottom). The differences in survival curves between the subgroups were significant ($P < 0.0001$) in all three modes of classification.

RESULTS

A total of 27,396 lymph nodes with a mean nodal yield of 41.8 ± 14.9 (mean ±SD) per specimen (range 20–113) were removed, of which 4,427 (16.2%) showed metastasis. Whether the number of resected nodes was below (group A) or above 40 (group B) did not affect survival for the patients in the current study ($P = 0.4307$) (Fig. 1). There was, however, an expected and significant difference in the number of metastatic nodes between the two groups (5.44 ± 7.24 for group A and 8.05 ± 11.48 for group B, $P = 0.0006$ by chi-square test). The correlation between the number of metastatic nodes and nodal metastatic rate was significant for both of the groups ($P < 0.0001$) (Fig. 2).

There was a significant difference in survival curves between each of the subgroups stratified by the anatomical extent of metastatic nodes (n categories). Five-year survival rates for each category were as follows: 78% (n = 196) for n0, 64% for n1 (n = 186) , 35% for n2 (n = 202), and 22% for greater than n3 (n = 72) ($P < 0.0001$). The same was true of the stratifications by the number of metastatic nodes (pN categories; 5-year survival rates of 78% for pN0, 62% for pN1, 34% for pN2, 16% for pN3, and 19% for pM1) and nodal metastatic rate (Fig. 3) ($P < 0.0001$). These results imply that any one of these lymph node staging scheme is feasible, provided the histopathologic evaluation is performed adequately.

The difference in survival curves between the groups A and B were not significant among any subgroup of patients stratified according to the n-categories or the rate of metastatic nodes (Fig. 4). By contrast, a significant and striking difference in the survival curves between the groups A and B was noted among the patients classified by the new TNM classification as pN2 ($P = 0.0082$) (Fig.

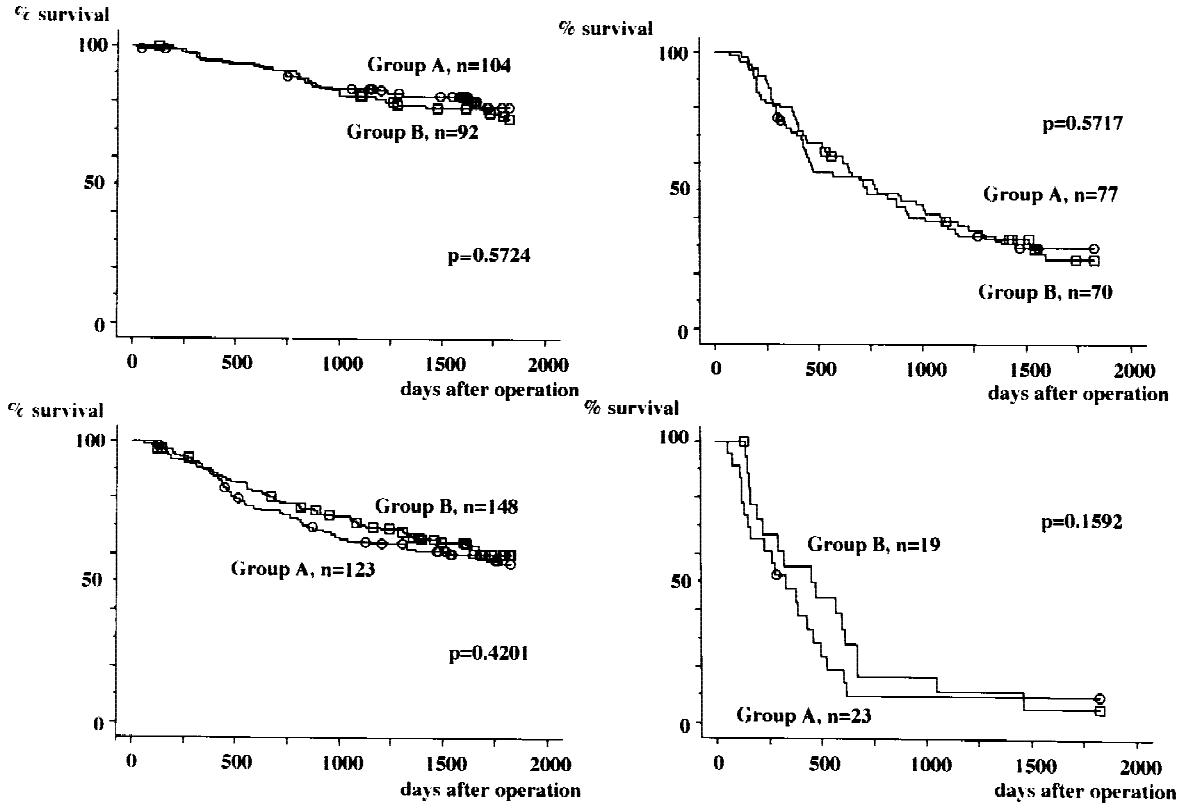

Fig. 4. Patients were stratified into four categories according to the lymph node metastatic rate. Top left: metastatic rate of 0%, n = 196. Bottom left: metastatic rate of 1–20%, n = 271. Top right: metastatic rate of 21–60%, n = 147. Bottom right: metastatic rate of > 60%, n = 42. For each category, patients were divided further into two groups according to the number of lymph nodes resected (groups A and B). No difference in the survival curves were observed between these two groups for any of the categories.

5). A likely explanation for this is that the greater nodal yield led to the detection of a greater number of metastatic nodes for group B patients, hence a tendency for group B patients to be up-staged in the new classification.

DISCUSSION

The extent of lymphatic involvement has been reported to reflect the aggressiveness of cancer cells and extensive nodal metastasis is known to represent poor survival [12]. Lymph node status assessment, therefore, is an essential part of stage classification for gastric carcinoma. This is performed in the recent edition of the TNM Classification by counting the number of metastatic lymph nodes [9]. One major concern for the new lymph node staging system is that the number of metastatic nodes is likely to be influenced by the number of lymph nodes resected and examined, because the likelihood of finding a metastatic node is considered to rise as the number of lymph nodes resected for histopathologic examination increases [13]. The higher probability of detecting nodal metastases with increasing nodal yields had been confirmed by the exponential model [14]. The nodal yields are considered to depend heavily on the extent of systemic lymphadenectomy and thoroughness of the lymph node retrieval [13]. Since the extent of lymphadenectomy varies greatly among institutions, so will the mean nodal yields. At institutions where the extended lymphadenectomy is not a standard procedure, the number of lymph nodes resected may be strictly limited, and the probability of detecting metastases will be correspondingly low. This will be the case in several Western institutions, as the much-awaited results of major randomized trials are unlikely to support extended D2 lymphadenectomy as a universally applicable procedure [5,6]. Less extensive lymphadenectomy and inadequately conducted examination of the specimens can both result in a decreased number of metastatic nodes, leading to stage migration. Under these circumstances, comparison of survival data between the East and the West based on the TNM classification can no longer be considered accurate.

The current study was performed in a Japanese institution where the extended lymphadenectomy is a standard procedure. Moreover, only cases with retrieval of greater than 20 lymph nodes were considered valid for the present analyses. Nevertheless, the number of metastatic nodes is still found to be affected by the nodal

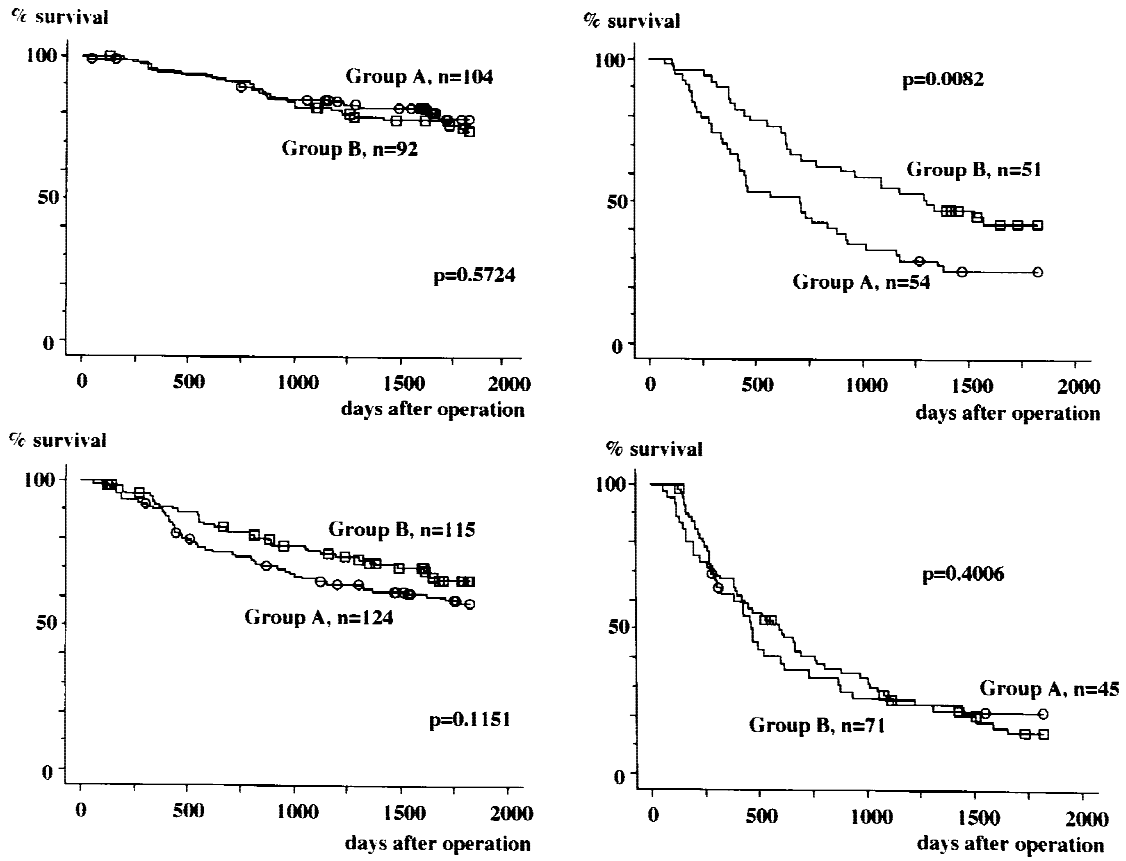

Fig. 5. Patients were stratified into four categories according to the number of metastatic nodes as specified in the 5th edition of the TNM Classification. Top left: pN0, n = 196. Bottom left: pN1, n = 239). Top right: pN2, n = 105. Bottom right: pN3 and pM1, n = 116. The patients in each category were divided further into two groups according to the number of lymph nodes resected (groups A and B). For pN2 (7–15 metastatic nodes), the difference in survival curves between groups A and B was statistically significant ($P = 0.0082$).

yield. While the effort to increase the nodal yield did not seem to affect survival (no difference in survival between the groups A and B, $P = 0.4307$), it did increase the probability to detect metastases, hence the significantly increased number of metastatic nodes for group B ($P = 0.0006$). Consequently, a difference in the number of lymph nodes harvested induced stage migration; the group B patients with greater nodal yields were likely to be up-staged when stratified according to the number of metastatic nodes. This was evident from the observation that the group B patients who belong to pN2 (7–15 metastatic nodes) were found to have a significantly ($P = 0.0082$) better survival than that of the group A patients who fell within the same category. Stage migration in the new TNM classification can thus result not only from the deficient lymph node yields due to limited lymphadenectomy, but also from varying lymph node yields, the reason for which is multifactorial. Such stage migration could render the TNM classification unreliable unless some measures are taken to circumvent it. One way to do this is to perform histologic examination of a fixed number of nodes for standardization [13,14]. In this case, the classification may become invalid for some patients whose nodal yield is too small. Our solution to the problem deduced from the current study is to make use of the lymph node metastatic rate, shown also to be a good prognostic indicator [10], as a parameter for the lymph node status assessment in the stage classification. Lymph node metastatic rate correlated significantly ($P < 0.0001$) with the number of metastatic nodes, a current parameter for pN categories in the new TNM classification. At the same time, it was found not to be affected by the nodal yield, as evident from the fact that the survival curves for groups A and B were almost identical for all the subgroups stratified according to the lymph node metastatic rate. Therefore, lymph node metastatic rate can be proposed as a novel parameter for lymph node status assessment, and similar analyses are warranted in the institutions with a sufficient number of cases but with divergent policies towards the extent of systematic lymphadenectomy.

REFERENCES

1. Kodera Y, Yamamura Y, Torii A, et al.: Postoperative staging of gastric carcinoma. A comparison between the UICC Stage Classification and the 12th Edition of the Japanese General Rules for Gastric Cancer Study. Scand J Gastroenterol 1996;31:476–480.

2. Kim JP, Kim YW, Yang HK, Noh D: Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. World J Surg 1994;18:872–877.
3. Hermanek P, Sobin LH (eds): ''UICC TNM Classification of Malignant Tumours.'' 4th Ed. New York: Springer-Verlag, 1992.
4. Japanese Research Society for Gastric Cancer (ed): ''Japanese Classification of Gastric Carcinoma.'' Tokyo: Kanehara Shuppan, 1995.
5. Bonenkamp JJ, Songun I, Hermans J, et al.: Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–748.
6. Cuschieri A, Fayers P, Fielding J, et al.: Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: Preliminary results of the MRC randomised controlled surgical trial. Lancet 1996,347:995–999.
7. Adachi Y, Kamakura T, Mori M, et al.: Prognostic significance of the number of positive lymph nodes in gastric carcinoma. Br J Surg 1994;81:414–416.
8. Wu CW, Hsieh MC, Lo SS, et al.: Relation of number of positive lymph nodes to the prognosis of patients with primary gastric adenocarcinoma. Gut 1996;38:525–527.
9. Sobin LH, Wittekind C (eds): ''TNM Classification of Malignant Tumours.'' 5th Ed. New York: John Wiley & Sons, 1997.
10. Kodera Y, Yamamura, Y, Shimizu Y, et al.: Metastatic paragastric lymph node rate is a significant prognostic factor for resectable stage IV gastric cancer. J Am Coll Surg 1997;185:65–69.
11. Hermanek P, Hutter RVP, Sobin LH, et al. (eds): ''TNM Atlas. Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours.'' Berlin: Springer, 1997.
12. Baba H, Korenaga D, Okamura T, et al.: Prognostic factors in gastric cancer with serosal invasion. Arch Surg 1989;124:1061–1064.
13. Bunt AMG, Hermans J, van der Velde CJ, et al.: Lymph node retrieval in a randomized trial on Western-type versus Japanese-type surgery in gastric cancer. J Clin Oncol 1996;14:2289–2294.
14. Bunt AM, Hogendoorn, PC, van de Velde CJ, et al.: Lymph node staging standards in gastric cancer. J Clin Oncol 1995;13:2309–2316.